Treatment Options After Discontinuation of Tysabri

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Agenda

- Why we use Tysabri
- Discuss the “Stratify” studies
  - JCV Antibody status
- Treatment Protocols
- Studies Discussing Medication Switches
- Case Studies

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Tysabri efficacy: Why we use it…

- TOP Study
  - Information presented at the 65th annual American Academy of Neurology, 2013
  - Long term Observational Study of Tysabri
  - Results from TOP indicates that post baseline Annual Relapse Rate for patients receiving Tysabri decreased from 1.99 at baseline to 0.28 after four years ($p < 0.0001$)
  - Disability remained stable as defined by the Expanded Disabilities Status Scale (EDSS)

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- Long-Term Safety and Efficacy and Association between Baseline Treatment
- History and Postbaseline Relapses in Multiple Sclerosis Patients Treated with Natalizumab in the TYSABRI
- Observational Program TOP (P04.134)

Stratify

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What is Stratify

- Stratify I & II are studies which had the primary aim(s) to establish the prevalence and identify the magnitude of risk of PML based on antibody status, among those patients who received Tysabri for treatment of Multiple Sclerosis.

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- Biogen-Idec ClinicalTrials.gov identifier NCT01070823

Stratify

- Prior to Stratify becoming available, there were creative infusion plans
- After Stratify, information on JCV antibody status became available
- Currently, Patient's risk are evaluated and treatment plans created

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Stratify I

- Stratify I was designed to define the prevalence of serum JC virus antibody in patients with Relapsing/Remitting Multiple Sclerosis (RMS) receiving or considering treatment with Tysabri.
- Started in 2010
- Ended in 2012

Biogen Idec sponsored study

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STRATIFY II

- Stratifying PML
  - Ongoing, longitudinal, observational study to analyze anti JCV antibody sero-prevalence among MS patients in the U.S.
  - The overall prevalence of anti-JCV antibodies was 53.5%

- 2012 AAN
- Anti-JCV Antibody Prevalence in Patients with Relapsing MultipleSclerosis Receiving or Considering Treatment with Natalizumab: Baseline Results of STRATIFY-2 (S42.002)

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Risk Groups and Treatment Protocols

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PML Risk

- Risk of PML lowest in anti-JCV antibody negative patients
- JCV negative showed <0.0001% chance of PML development (ref#)
- PML risk highest in patients with JCV antibody positive status, prior immunosuppressant use and 24-48 months of Tysabri treatment
- 10.6 cases per 1000 patients treated

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- Anti-JCV Antibody Prevalence in Patients with Relapsing Multiple Sclerosis Receiving or Considering Treatment with Natalizumab: Baseline Results of STRATIFY-2(S41.002)

Identifying High Risk Patients

- First High Risk Group Identified
  - JCV status
  - Length of time on Tysabri infusions
  - Prior Immunosuppressant use

Biogen Idec Stratify 1 and Stratify 2

Clinical trials .gov

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Identifying High Risk Patients

- Further development of Risk Group:
- Low Body Weight
  - European Study
    - Looked at 64 kg, with a mean of 70 kg with no significant difference
  - U.S. Study
    - Median weight of 78 kg, then divided into weight categories
    - 13% fell into the 60 kg or less category
- There is a striking PML increase in the lowest weight category 3x> from the US
- And 2x> US and EU

- (Foley, J. AAN 2013; abstract S230.002)

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Articles showing rebound after discontinuation of Tysabri and Medication SWITCHES

- Discuss Article by West and Cree on Tysabri drug suspension
- Review Wash out period after discontinuation of Tysabri prior to starting MS oral therapies
- Review Abstract Dr. Chinea regarding initiation of GA after discontinuing Tysabri

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- West, T., Cree, B., (2010) Natalizumab Dosage Suspension: Are we Helping or Hurting?
  - *ANN NEUROL 68;395-399*
- AFFIRM TRIAL
- Abstract Dr. Chinea

Case studies

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Introduction to Case Studies

- 5 case studies
- All JCV anti-body positive
- Discontinuation based on patient choices due to positive JCV status
- Results from Stratify studies were not available at the time of decision
- 4 started on Copaxone at the time of discontinuation
- MRI's were taken post-discontinuation at 4-12 months

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Case Study (Patient Zero)

- A 33 year old patient prior to Stratify who had been on Tysabri for more than 18 months.
- A Drug Holiday was suggested and she was going to resume a DMT for 6 mos.
- Patient did not start DMT and presented at five months with relapse symptoms and five new GAD enhancing T2 brain Lesions
- Relapse symptoms were:
  - Vertigo and
  - Double Vision
  - LP to evaluate for JCV negative

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Protocol after discontinuing Tysabri

- Week four after Tysabri d/c
- Start Acthar GEL 80 units SQ QD x 5 days every 3 months
- Start on DMT
- Continue for six months

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ACTHAR GEL OR SOLUMEDROL

- Either could potentially be used
- In the five cases that we will discuss

  Previous Poor tolerance to IV SoluMedrol

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Case Studies

- 44 year old Caucasian female
- Disease duration 6 years
- Acthar Gel 80 units SQ QD x 5 days started 4 weeks after Tysabri dc
- Started Copaxone week 4 after Tysabri dc
- Pulses of Acthar x 3 months
- Copaxone x 6 months, MRI at 6 months unchanged

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Case Study

- 37 year old Caucasian female
- Disease duration 3 years
- Same protocol (including Copaxone)
- MRI at four months unchanged
- No change in EDSS

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Case Study

- 35 year old African American female
- Disease Duration 5 years
- Same protocol (including Copaxone)
- MRI at 6 months unchanged
- No change in EDSS score

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Case Study

- 57 year old Caucasian female
- Disease Duration 8 years
- Same protocol (including Copaxone)
- MRI at 8 months unchanged
- No change in EDSS score

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Case Study

- 45 year old Caucasian male
- Disease Duration 13 years
- Had been on several Disease Modifying Therapies (DMT) and would not go back on an injection
- IVIG at 6 weeks (no Copaxone)
- MRI at 7 months unchanged
- No change in EDSS score

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Limitations and Caveats

- Off label use of ACTHAR
- Retrospective Case studies (limited statistical information)
- MRI's not at consistent time points

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Conclusions

- Using the protocol of ACTHAR Gel and Copaxone OR IVIG
  - There were NO clinical relapses or changes in EDSS score
  - NO new T2 enhancing brain lesions

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References

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